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Abstract: Hepatocellular carcinoma (HCC) is one of the major health problems worldwide, and continues to grow because of its association with hepatitis B and C viruses. In patients with HCC, liver transplantation (LT) and liver resection are the only two curative treatment options. LT remains the best option since it not only removes the tumor, but also the underlying disease. The prerequisite for long-term success of LT for HCC depends on the tumor load and strict selection criteria with regard to the size and number of existing HCC lesions. The need to obtain the optimal benefit from a limited number of grafts has prompted the implementation of well-defined selection criteria that identify patients with early HCC who may benefit from better long-term outcome after LT. Unfortunately, LT can only be proposed in approximately 30% of patients with HCC due to limitations in donor graft availability. In this particular setting, open and laparoscopic surgical resection represent reasonable treatment modalities in noncirrhotic HCC patients. The decision-making process for liver resection should integrate the tumor stage, quality and function of the underlying liver parenchyma, volume of the future liver remnant, and general condition of the patient. In patients with favorable features (solitary tumor, compensated Child-Pugh A cirrhosis, no portal hypertension), the reported 5-year survival rates range between 50 and 70%. In specific cases, liver resection and LT may be combined in the same patient.

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Multimodal Treatment Strategies in Patients Undergoing Surgery for Hepatocellular Carcinoma

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Key Words
Cirrhosis · Surgical resection · Liver transplantation

Abstract
Hepatocellular carcinoma (HCC) is one of the major health problems worldwide, and continues to grow because of its association with hepatitis B and C viruses. In patients with HCC, liver transplantation (LT) and liver resection are the only two curative treatment options. LT remains the best option since it not only removes the tumor, but also the underlying disease. The prerequisite for long-term success of LT for HCC depends on the tumor load and strict selection criteria with regard to the size and number of existing HCC lesions. The need to obtain the optimal benefit from a limited number of grafts has prompted the implementation of well-defined selection criteria that identify patients with early HCC who may benefit from better long-term outcome after LT. Unfortunately, LT can only be proposed in approximately 30% of patients with HCC due to limitations in donor graft availability. In this particular setting, open and laparoscopic surgical resection represent reasonable treatment modalities in noncirrhotic HCC patients. The decision-making process for liver resection should integrate the tumor stage, quality and function of the underlying liver parenchyma, volume of the future liver remnant, and general condition of the patient. In patients with favorable features (solitary tumor, compensated Child-Pugh A cirrhosis, no portal hypertension), the reported 5-year survival rates range between 50 and 70%. In specific cases, liver resection and LT may be combined in the same patient.

Background

Hepatocellular carcinoma (HCC) is one of the major health problems worldwide, and continues to grow because of its association with hepatitis B and C. The diagnosis and treatment of HCC has witnessed major changes over the past decade. Until the early 1990s, HCC was a relatively rare malignancy that was typically diagnosed at an advanced disease stage. Nowadays, HCC represents the fifth most common malignancy worldwide and its mortality is third among all solid tumors, behind carcinomas of the lung and the colon [1]. Despite recent improvements in screening, detection, surgical treatment and chemotherapy, the overall survival (OS) and recurrence-free survival of patients with HCC remains lower than that for most other solid tumors [1, 2]. HCC typi-

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cally presents at an advanced stage with only a limited portion of cases being suitable for curative treatment strategies, some of which include surgical resection, liver ablative procedures and liver transplantation (LT) [3]. Unfortunately, most patients are seen when the disease has reached a stage beyond curative treatment, leaving palliative care as the only alternative [4–6]. This review will focus on the different medical and surgical treatment modalities in patients with HCC and will provide background to clinical cases presented at the Falk Symposium in Mainz, Germany 2012.

Surgical Resection for HCC

Among curative treatment options for HCC, liver resection and transplantation are considered the mainstay of curative therapy [7]. However, LT can only be proposed in approximately 30% of patients with HCC due to limitations in donor graft availability and transplant criteria in this particular setting [3]. The selection of the primary treatment for HCC depends on tumor stage, functional status of the liver and the general condition of the patient. When the liver parenchyma is normal, which is the less frequent situation, the treatment of choice consists of surgical resection. However, most patients with HCC have an underlying chronic liver disease at the time of diagnosis. In this situation, LT is considered as the treatment of choice because it treats both the tumor and the underlying disease. Unfortunately, while progress has been made in the detection and screening of HCC, the low availability of liver grafts has been a major problem and many patients die on the waiting list. As such, liver resections also in patients with underlying chronic liver disease are becoming increasingly popular. This is attributed to the development of new surgical techniques and better preoperative assessment of patient risk factors associated with partial hepatectomy in this particular setting [8, 9]. To consider a liver resection in patients with HCC, three factors need to be integrated in the process of decision-making: (1) tumor stage, (2) quality and function of the underlying liver parenchyma, and (3) volume of the future liver remnant.

(1) In general, solitary HCC lesions confined to the liver without vascular invasion with well-preserved hepatic function have the best outcomes. Although there are no strict criteria in terms of tumor size, tumor-associated predictors of poor outcome after liver resection include satellite nodules, size of lesion >5 cm, serum α-fetoprotein level >2,000 ng/ml, positive resection margins and Union for International Cancer Control (UICC) stages III or IV [10].

(2) Almost 90% of HCC develop in patients with chronic underlying liver disease (hepatitis B, hepatitis C, alcoholic liver disease, hemochromatosis and nonalcoholic steatohepatitis). Importantly, the risk of resection in these patients is directly related to a decrease in the capacity of the remnant liver to regenerate [2]. As such, preoperative assessment of the underlying liver disease is of upmost clinical importance and is usually performed using the Child-Pugh classification with the addition of quantitative liver function tests that have been developed to refine patient selection in this setting. Based on regional practice patterns that vary around the world, one of the most commonly used tests in this setting is the indocyanine green (ICG) clearance test. In fact, ICG, a tricarbocyanine dye that is completely and exclusively cleared by hepatocytes, is excreted into the bile in unmodified form and does not enter the enterohepatic circulation. As such, hepatectomy is possible in patients with less than 15% ICG retention, whereas patients with more than 20% ICG retention should be limited to minor or no resections [11]. In this setting, it is particularly important to assess portal vein hypertension (PVH), as PVH is another important risk factor for postoperative liver failure and is usually considered a contraindication for major liver resection. Assessment of PVH can be achieved preoperatively by invasive hepatic vein catheterization, upper endoscopy (esophageal varices) and triphasic preoperative CT imaging (splenomegaly and/or venous collateral channels). In order to determine the presence or absence of cirrhosis, hepatic vein catheterization may be combined with transjugular liver biopsy of the nontumorous liver.

(3) Assessment of the future liver remnant volume is performed by CT volumetry. Whereas young patients with no underlying liver disease may undergo resection of up to 75% of the total liver volume, patients with chronic liver disease may undergo resections of more than 40–50% of the total liver volume.

Orthotopic Liver Transplantation for HCC

HCC was one of the first indications for LT because it was postulated that this approach would not only eliminate the tumor, but would also cure the underlying liver disease. However, early experience with LT for HCC in the 1980s was disappointing due to relatively high recurrence rates (>50%) and discouraging 5-year OS results

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ranging from 10 to 35% [12]. Since it appeared obvious that the success of LT for HCC depends on tumor load, strict selection criteria with regard to the size and number of tumor nodules [Milan criteria (MC): single HCC nodule <5 cm or with up to 3 nodules <3 cm without macrovascular invasion] allowed achieving a 5-year OS of more than 70% and a 5-year recurrence rate of less than 10% [13]. This evolution is mainly due to improvement of imaging techniques and surveillance programs that have been widely introduced; therefore, HCCs are being detected earlier at a stage at which effective treatment is feasible. In this context, LT for HCC currently represents 25 and 35% of the indications for LT in Europe and the USA, respectively. The need to obtain the optimal benefit from the limited number of organs that are available has prompted the maintenance of selection criteria in order to list only those patients with early HCC who have the highest likelihood of survival after LT.

Both tumor size and number are important factors of posttransplant recurrence inherent to the biology of HCC tumor that should be taken into account whenever selecting HCC patients beyond MC for LT. This has been well described and demonstrated in the 'Metroticket' concept (the farther you go in expansion of HCC staging criteria for selection for LT, the more you have to pay in terms of higher recurrence rates and poorer survival) [14]. This model, based on the analysis of 1,556 patients transplanted at 36 centers, provides a linear correlation between tumor diameter and recurrence throughout the observed range. Survival was directly correlated with the size of the largest tumor, number of tumors and presence of microvascular invasion at explant pathology. Patients who fell within the 'up to 7 criteria' (HCC with 7 as the sum of the largest tumor diameter in cm and number of tumors) and without microvascular invasion achieved a 5-year OS of 71%. These 'up to 7 criteria' were compared with the Milan and University of California San Francisco criteria (1 tumor ≤6.5 cm, or 2–3 nodules ≤4.5 cm with total tumor diameter ≤8 cm) in a pathological study [15]. The 'Metroticket' performed the best as a staging system with 5-year recurrence rate of 4% in patients within and 51% in patients beyond those 'up to 7 criteria'. However, this staging system is difficult to use in practice since the microvascular invasion cannot be accurately assessed by any preoperative work-up.

The last international consensus conference on LT for HCC concluded that MC are currently the benchmark for selection of HCC patients for LT. A modest expansion of the number of potential candidates may be considered on the basis of the last studies reported above [16].

Medical and Interventional Treatment

The majority of patients with HCC present with a disease stage beyond curative treatment (surgical resection or LT), leaving palliative care as the only alternative. Available medical and interventional treatment options depend on the size, number and location of tumors; presence or absence of underlying liver disease (fibrosis, cirrhosis, portal hypertension); associate operative risk based on extent of underlying liver disease and comorbid diseases; overall performance status of the patient; patency of portal vein, and presence of metastatic disease.

Local Ablative, Bridging and Downstaging Therapies

For patients with advanced HCC who are not candidates for curative treatment, local therapies such as transarterial chemoembolization (TACE)/transarterial radioembolization (TARE), ethanol, radiofrequency and cryoablation, as well as systemic chemotherapy remains the mainstay of therapy. Local ablative therapies are defined as the direct application of chemical or thermal therapies to a specific focal tumor in an attempt to achieve eradication or substantial tumor destruction. In patients with HCC, tumor ablative procedures are usually performed with a percutaneous image-guided approach. Intratumoral injections of ethanol, heat (via radiofrequency or microwave) or cold (cryoablation with liquid nitrogen) may be used to control tumors smaller than 4–5 cm. In general, these procedures are reserved for patients who do not meet the criteria for primary surgical resection, yet are candidates for a liver-directed procedure and/or LT.

Radiofrequency ablation (RFA) is the delivery of radiofrequency thermal energy to the HCC lesion causing necrosis of the tumor. During RFA, a high-frequency alternating current is delivered from the tip of an electrode into the surrounding tissue. The ions within the tissue attempt to follow the direction of the alternating current resulting in friction and eventual heating of the tissue. As the tissue temperature elevates above 60°C, tumor cells begin to die resulting in an area of tumor necrosis. RFA can be performed surgically (laparotomy or laparoscopy) or interventionally (image-guided percutaneous approach), and is the most commonly used local ablation modality in the treatment of patients with HCC lesions less than 4 cm in size [17]. As such, some studies show good initial tumor control with an average local recurrence rate of 5–6% within the first 20 months [18]. Even though recent reports on long-term outcome of RFA-treated patients have shown that patients with Child-Pugh A liver disease and early-stage HCC show 5-year

survival rates of as high as 50–70%, and may even reach 76% in patients who meet the Barcelona Clinic Liver Cancer (BCLC) Classification criteria for surgical resection [19, 20], a recent randomized controlled trial comparing resection versus RFA alone in patients within the MC has demonstrated superior OS for the surgical arm (5-year survival: 75% for surgical resection vs. 54% for RFA; $p = 0.001$) [21].

TACE is a widely used palliative treatment for patients with HCC and employs the injection of an anticancer drug (Adriamycin or cisplatin), mixed with Lipidol into the hepatic artery or one of its branches, followed by arterial embolization using Gelfoam particles or powder [5]. Clinically, HCC tends to get its vascularization from the hepatic artery and for that reason TACE has proven to be effective in managing many patients with localized disease [2, 22]. When mixed with Lipidol, Adriamycin and cisplatin are supposed to form a stable mixture that stays in close contact with the tumor for several weeks, thus enhancing the antitumor effect of the selected anticancer agent. In addition, Lipidol contributes to the embolization of arterial vessels inside the tumor, and thereby helps to retain the cytotoxic drug in the tumor [23].

TARE is a locoregional therapy, but has – in contrast to chemotherapy – the ability to destroy liver tumors regardless of histologic origin. Because of the high radiosensitivity of liver tissue and the fact that the liver moves during breathing, external beam radiation has had a limited role in treating liver disease despite recent technological advances [24]. In contrast, with internal radiation through local delivery of yttrium-90 microspheres (radioembolization) into the arterial circulation, a radiation dose high enough for tumor control (70–90 Gy) may be delivered to the tumor without extensive damage to the surrounding nontumorous liver. Radioembolization in the treatment of liver tumors has attracted significant interest over the last decade both for the treatment of nonresectable HCC as well as downsizing before resection and LT [25]. The overall tumor response rates in patients with HCC yield from 78 to 89% [26]. Even though no randomized controlled trial has yet to compare TARE versus TACE, two retrospective series did not observe a difference in OS between the two groups, despite a longer progression-free survival in the TARE group [27, 28]. The advantages of TARE as a costly and complex procedure need to be determined in prospective clinical trials.

Bridging strategies circumscribe locoregional therapies employed in patients already on the waiting list for LT. Bridging strategies have been introduced to reduce waiting list mortality when transplantation cannot be administered immediately. In addition, interest concerning LT of patients with HCC beyond the MC has shifted lately from expanded criteria to tumor downstaging, generally by nonsurgical means, to reduce the size and/or number of tumors from beyond to within MC. As such, several strategies have been adopted lately as bridging therapies: TACE/TARE, RFA or resection.

The rationale for using TACE as a neoadjuvant therapy prior to LT is twofold: to control tumor growth while the patient is on the waiting list and to induce tumor necrosis that may reduce tumor dissemination during LT. Overall, it has been shown that TACE – while not increasing the complication rate for LT – does not improve OS after LT neither for early nor for advanced HCC [22]. As such, a retrospective case control study investigated the results of TACE on outcome after LT [29] and found no significant difference in the 5-year survival rate (69% with TACE vs. 64% without TACE), even though tumor recurrences were less frequent in the TACE/LT group (13 vs. 23%). Therefore, it appears that TACE is not harmful and may allow reducing dropout rates from the waiting list.

In pathological studies, the results of RFA appear to be superior to TACE in terms of local tumor control [30, 31]. Mazzaferro et al. [32] showed in patients who underwent RFA as a bridge treatment to LT that tumor size greater than 3 cm or the presence of large abutting vessels result in a drop of the rate of complete tumor necrosis to 50% or less. Thus, RFA appears to be safe as a bridging therapy for HCC less than 3 cm. However, its effect to decrease the dropout rates still needs to be proven in further prospective trials. Radioembolization represents 5–10% of bridging locoregional treatment in the organ procurement and transplant network registry, but data available on its impact are scarce and further experience is needed [33]. In a recent study looking at the radiopathological correlation of HCC treated with internal radiation using yttrium-90 microspheres, all targeted lesions had some histologic necrosis and 60% of them showed complete necrosis [31].

In compensated cirrhotic patients with HCC and a long anticipated time on the waiting list, liver resection followed by listing for LT could be applied [33]. The decision for resection depends on liver function and the size and location of the tumor. This strategy allows control of the tumor and a better assessment of its pathological features. In case of bad prognosis factors (poor differentiation, microvascular invasion, absence of capsule), a preemptive LT (bridge LT) could be advised (i.e. before recurrence but after sufficient observation). If the tumor does not show any risk factors for recurrence, LT may be postponed and offered only in cases of tumor recurrence

(salvage LT). Liver resection for small solitary HCC in compensated cirrhosis yields an OS rate comparable to LT [34]. Despite a significant recurrence rate, close imaging monitoring after liver resection allows salvage LT in two thirds of the patients with recurrence in intention-to-treat analysis [34].

Bridging strategies with locoregional treatments are probably beneficial in patients when a long waiting time is likely because it decreases dropout rates without impairing posttransplant outcomes. This strategy seems to be indicated for T2 tumor (solitary tumor with vascular invasion or multiple tumors none more than 5 cm) and patients likely to wait longer than 6 months [33]. Pathological studies suggest that there is a marginal advantage for RFA in terms of local ablation. Newer strategies combining TACE and RFA or using yttrium-90 may be promising. Finally, liver resection followed by salvage LT in case of recurrence should be restricted to patients with favorable oncological factors.

Systemic Chemotherapy and Targeted Agents

For patients with advanced HCC who are not candidates for surgical resection, LT or localized ablative therapies, systemic chemotherapy has never shown a significant advantage compared to best supportive care. Unfortunately, HCC is a relatively chemoresistant tumor with response rates as low as 10% for single-agent chemotherapy. Doxorubicin has initially been licensed for the use as first-line treatment in unresectable HCC. Even though being the standard of care for decades, doxorubicin is usually not well tolerated and seems to be less effective in HCC patients with underlying liver disease. Recently cisplatin-based combination regimens have been shown to improve response rates to up to 20%, but to date, no survival advantage as compared to best supportive care could be shown [35]. Moreover, some of these regimens cause considerable toxicity and are therefore not well tolerated, especially in patients with cirrhosis and other comorbid diseases.

Targeted agents or antiangiogenesis agents (sorafenib, bevacizumab, cetuximab) have recently been employed or tested in the treatment of advanced HCC [6]. Only sorafenib, a small-molecule multityrosine-kinase inhibitor, has been shown to extend survival in patients with advanced HCC and has opened the door for other possible adjuvant antiangiogenic treatment strategies (SHARP trial) [36]. However, the median survival improvement of 2.8 months (in the Western world [37]) and 1.7 months (in the Eastern world [38]) is, to many outside the field of oncology, regarded as marginal. Currently, sorafenib is the only FDA-approved antineoplastic agent for HCC [39].

Conclusion

Due to the actual allocation system based in Europe and the United States, not all patients with HCC occurring in normal liver or in an underlying chronic liver disease can have access to LT. Therefore, liver resection has taken an important place in the curative treatment for HCC. This surgery can be performed safely providing that the liver function was not previously altered and there is adequate future liver remnant volume and absence of portal hypertension. If the waiting time for LT is predicted to be prolonged, the risk of tumor progression and either dropout from the list or interval dissemination with posttransplant tumor recurrence is recognized. Then liver-directed therapy like TACE, TARE, RFA or microwave ablation should be used to decrease these risks, and resection and LT should be associated rather than opposed.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

References

1 Siegel R, Naishadham D, Jemal A: Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
2 Clavien PA, Petrowsky H, DeOliveira ML, Graf R: Strategies for safer liver surgery and partial liver transplantation. N Engl J Med 2007;356:1545–1559.
3 Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. Lancet 2003;362:1907–1917.
4 Lin S, Hoffmann K, Schemmer P: Treatment of hepatocellular carcinoma: a systematic review. Liver Cancer 2012;1:144–158.
5 Lencioni R: Chemoembolization in patients with hepatocellular carcinoma. Liver Cancer 2012;1:41–50.
6 Kudo M: Treatment of advanced hepatocellular carcinoma with emphasis on hepatic arterial infusion chemotherapy and molecular targeted therapy. Liver Cancer 2012;1:62–70.
7 Belghiti J, Fuks D: Liver resection and transplantation in hepatocellular carcinoma. Liver Cancer 2012;1:71–82.

8 Slankamenac K, Breitenstein S, Held U, Beck-Schimmer B, Puhan MA, Clavien PA: Development and validation of a prediction score for postoperative acute renal failure following liver resection. Ann Surg 2009;250:720–728.
9 Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, Wong J: Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg 2001;234:63–70.
10 McCormack L, Petrowsky H, Clavien PA: Surgical therapy of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2005;17:497–503.
11 Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, Takayama T, Makuuchi M: One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003; 138:1198–1206, discussion 1206.
12 Iwatsuki S, Gordon RD, Shaw BW Jr, Starzl TE: Role of liver transplantation in cancer therapy. Ann Surg 1985;202:401–407.
13 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
14 Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, et al: Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.
15 D'Amico F, Schwartz M, Vitale A, Tabrizian P, Roayaie S, Thung S, Guido M, del Rio Martin J, Schiano T, Cillo U: Predicting recurrence after liver transplantation in patients with hepatocellular carcinoma exceeding the up-to-seven criteria. Liver Transpl 2009;15: 1278–1287.
16 Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A: Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11–e22.
17 Lencioni R, Crocetti L: Radiofrequency ablation of liver cancer. Tech Vasc Interv Radiol 2007;10:38–46.
18 Curley SA, Izzo F, Ellis LM, Nicolas Vauthey J, Vallone P: Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000;232:381–391.
19 Choi D, Lim HK, Rhim H, Kim YS, Lee WJ, Paik SW, Koh KC, Lee JH, Choi MS, Yoo BC: Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. Eur Radiol 2007;17:684–692.
20 N'Kontchou G, Mahamoudi A, Aout M, Ganne-Carrie N, Grando V, Coderc E, Vicaut E, Trinchet JC, Sellier N, Beaugrand M, et al: Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 2009;50:1475–1483.
21 Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y: A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010;252:903–912.
22 Lesurtel M, Mullhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA: Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: an evidence-based analysis. Am J Transplant 2006;6:2644–2650.
23 Yamashita Y, Takahashi M, Fukushima S, Nishida M, Nakano M: Experimental study of hepatic artery embolization: evaluation of various embolic materials. Radiat Med 1987; 5:75–82.
24 Schwarz RE, Abou-Alfa GK, Geschwind JF, Krishnan S, Salem R, Venook AP, American Hepato-Pancreato-Biliary Association, Society of Surgical Oncology, Society for Surgery of the Alimentary Tract: Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement. HPB (Oxford) 2010;12:313–320.
25 Kennedy AS, Salem R: Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies. Cancer J 2010;16:163–175.
26 Vente MA, Wondergem M, van der Tweel I, van den Bosch MA, Zonnenberg BA, Lam MG, van Het Schip AD, Nijsen JF: Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Eur Radiol 2009;19:951–959.
27 Kooby DA, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, Staley CA 3rd, Kim HS: Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2010;21:224–230.
28 Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, et al: Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138: 52–64.
29 Porrett PM, Peterman H, Rosen M, Sonnad S, Soulen M, Markmann JF, Shaked A, Furth E, Reddy KR, Olthoff K: Lack of benefit of pretransplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. Liver Transpl 2006;12:665–673.
30 Pompili M, Mirante VG, Rondinara G, Fassati LR, Piscaglia F, Agnes S, Covino M, Ravaioli M, Fagiuoli S, Gasbarrini G, et al: Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: assessment of efficacy at explant analysis and of safety for tumor recurrence. Liver Transpl 2005;11: 1117–1126.
31 Riaz A, Kulik L, Lewandowski RJ, Ryu RK, Giakoumis Spear G, Mulcahy MF, Abecassis M, Baker T, Gates V, Nayar R, et al: Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. Hepatology 2009;49:1185–1193.
32 Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, Sarli D, Schiavo M, Garbagnati F, Marchiano A, et al: Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg 2004;240:900–909.
33 Majno PE, Lencioni R, Mornex F, Girard N, Poon RT, Cherqui D: Is treatment of HCC on the waiting list necessary? Liver Transpl 2011; 17(Suppl 2):S98–S108.
34 Cherqui D, Laurent A, Mocellin N, Tayar C, Luciani A, Van Nhieu JT, Decaens T, Hurtova M, Memeo R, Mallat A, et al: Liver resection for transplantable hepatocellular carcinoma: long-term survival and role of secondary liver transplantation. Ann Surg 2009;250:738–746.
35 Zhu AX, Blaszkowsky LS, Ryan DP, Clark JW, Muzikansky A, Horgan K, Sheehan S, Hale KE, Enzinger PC, Bhargava P, et al: Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24:1898–1903.
36 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
37 Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB: Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. JAMA 2010;304:2154–2160.
38 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
39 National Comprehensive Cancer Network. NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 2.2008). http://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf.